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| 09/497,591 | 02/03/2000 | Gary L. Nelsestuen | 09531-016001 | 7689 |

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ELI LILLY AND COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

| EXAMINER |
|---|
| SCHNIZER, HOLLY G |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | 15 |

DATE MAILED: 10/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/497,591 | Applicant(s) NELSESTUEN, GARY L. | |
|---|---|---|---|
| | Examin r Holly Schnizer, Ph.D. | Art Unit 1653 | |

*-- Th MAILING DATE of this communication appears on the cover sh t with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *Paper #14, filed June 14, 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8-14 and 61-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-14 and 61-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of the Claims*

The Amendment and Response filed June 14, 2002 has been entered and considered. Claims 1-7 and 15-60 have been cancelled. Claims 61-75 have been added. Therefore, Claims 8-14 and 61-75 are pending.

### *Drawings*

The drawings filed May 31, 2002 have been approved by the Draftsperson.

### *Objections*

The Specification is objected to for failing to comply with the sequence rules. The Specification refers to amino acid sequences of greater than 4 amino acids at p. 11, Table 1; page 12, Table 2; p. 13, Table 3; p. 14, Table 4; and p.39, lines 28-32 to p. 40, lines 1-2. 37 C.F.R. 1.821(d) states "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application" (see MPEP 2422 and 37 C.F.R 1.821). Correction is required.

Claims 8, 73, 74, and 75 are objected to because of the following informalities: "Gla" should be re-written as – GLA –. Appropriate correction is required.

***Objections/Rejections Withdrawn***

The objection of Claims 8-14 for depending from non-elected Claim 1 is withdrawn in light of the amendment to Claim 8. Correction is required.

The objection of Claim 12 is withdrawn in light of the amendment to the claim.

The rejection of Claims 8-14 as indefinite for the recitation of "corresponding native vitamin K-dependent polypeptide" in Claim 1 is withdrawn in light of the amendment to the claims.

The rejection of Claims 8, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hashimoto et al. (EP 0 354 504, 1990; Ref. AN of IDS filed Oct. 30, 2001 as Paper No. 5) is withdrawn in light of the amendment to Claim 8 providing the limitation that the GLA domain comprises at least 35 unsubstituted residues corresponding to SEQ ID NO:1. The protein C polypeptide of Hashimoto et al. contains a Gla domain sequence of factor X. The factor X sequence has more than 35 amino acid residues that differ from the sequence of SEQ ID NO:1, therefore, the factor X sequence is considered to have less than 35 unsubstituted amino acids corresponding to the sequence of SEQ ID NO:1.

The rejection of Claims 8, 9, and 14 under 35 U.S.C. 102(e) as being anticipated by Smirnov et al. (U.S. Patent No. 5,837,843; Reference AI of IDS filed Oct. 30, 2001 as Paper No. 5) is withdrawn in light of the amendment of Claim 8 adding that the modified Gla domain must have at least 35 unsubstituted residues corresponding to SEQ ID NO:1 (human protein C amino acid sequence). The Gla domain of prothrombin (substituted into the protein C polypeptide of Smirnov et al.) has less than 35 residues that would be considered unsubstituted relative to SEQ

ID NO:1 (i.e. the prothrombin Gla domain has more than 10 residues that are not identical to the Gla sequence of SEQ ID NO:1).

The rejection of Claims 8, 9, and 14 under 35 U.S.C. 102(b) as being anticipated by Wakako et al. (EP 0 296 413, 1988; Ref. AM Of IDS filed Oct. 30, 2001 as Paper No. 5) is withdrawn in light of the amendment to the claims. The Gla domain of bovine protein C has more than 10 amino acids that are different to that of SEQ ID NO:1 (sequence of the Gla domain from human). Therefore, the human C hybrid polypeptide containing the Gla domain of bovine protein C described in Wakako et al. is considered to have less than 35 unsubstituted residues corresponding to SEQ ID NO:1.

***Rejections Maintained***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-14 are indefinite as to what sequence the phrase "at amino acid 12" (claim 9), "at amino acid 33" and "at amino acid 34" (claim 10), "at amino acid 35" (claim 11), "at amino acid 36" (claim 12), "at amino acid 11" (claim 13), and "at amino acid 29" (claim 14) refers. There is no reference point for the amino acid position at which the substitution is made. Correction is required.

Applicants argue that the claims were amended to include a reference point. This argument has been considered but is not deemed persuasive. The claims are confusing as to what sequence the amino acid positions refer. Is amino acid 12 the position in protein C? Since

the claims are drawn to protein C and activated protein C, the claims would be much clearer if written to only refer to substitutions in protein C sequences. Thus, the examiner suggests deleting references to the amino acid positions (given above) that do not have reference sequences. For example, Claim 9 could be amended to read "...wherein said amino acid substitution comprises a glycine residue at amino acid position 11 of SEQ ID NO:1." . Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 and new Claims 61-63 and 75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein C or activated protein C (APC) polypeptide comprising a modified GLA domain, wherein the modified Gla domain comprises at least one substitution that increases membrane binding affinity of said polypeptide relative to a protein C or APC polypeptide of identical sequence except for the substitution, wherein said amino acid substitutions comprise the specifically claimed substitutions at specifically claimed positions as in Claims 9-14, does not reasonably provide enablement for any protein C or APC from any source (human or bovine for example) comprising a GLA domain with any number of substitutions or any positions substituted that has the claimed activity, or no activity at all (see Claim 61). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Response to Applicants Arguments:

Applicants argue that the specification provides examples of amino acids that can be substituted in the Gla domain of protein C, teaches how to make the polypeptides of the

invention, and describes techniques for determining membrane affinity of protein C polypeptide and a test for determining if a particular amino acid substitution enhance membrane binding and activity of the polypeptide.

These arguments have been considered but are not deemed persuasive. As stated in the previous Office Action (Paper No. 11) and repeated below, the specification presents a proposed model on which to select specific modifications to enhance membrane binding affinity. However, the model does not appear to make any predictions on protein function (enhanced activity is one of the limitations of the claims). Moreover, the model only addresses substitutions of surface amino acids (particular amino acid positions) to negatively charged amino acids and does not address making substitutions to any amino acid at any position within the Gla domain. As explained in the previous Office Action and below, the state of the art is such that it is acknowledged that amino acid modifications of proteins is unpredictable. With respect to Applicants argument that the claimed modifications may be tested for activity, this is not adequate guidance as to the nature of the protein C polypeptides that may be constructed, but is merely an invitation to the artisan to use the disclosed protein as a starting point for further experimentation. Thus, as stated in the previous Office Action:

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 8 is drawn to a protein C or activated protein C (APC) from any source (human or bovine for example) comprising any number of modifications in the GLA domain that enhance membrane binding affinity and activity of the polypeptide.

The specification provides working examples of the specific bovine and human protein C or activated protein C polypeptides with the following mutations (relative to SEQ ID NO:1):

Through sequence comparisons of various members of the Vitamin K dependent protein family, observations of membrane binding of Vitamin K dependent protein family members and a number of specific protein C and APC mutants, the specification proposes a contact site archetype. The model predicts a correlation between membrane affinity and a net negative charge on the residues that are located on the surface of the protein (see Figure 11 and Example 5, beginning at p. 37) and that the closer a member of the protein family approaches this electrostatic pattern, the higher its membrane affinity. Thus, the specification presents a proposed model on which to select specific modifications. However, the model does not appear to make any predictions on protein function (enhanced activity is one of the limitations of the claims). Moreover, the model only addresses substitutions of surface amino acids (particular amino acid positions) to negatively charged amino acids and does not address making substitutions to any amino acid at any position within the Gla domain.

The state of the art is such that it is acknowledged that amino acid modifications of proteins is unpredictable. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. The instant claims encompass proteins which have any number of amino acid substitutions within the Gla domain. However, the specification does not provide guidance of what amino acids may be changed to increase both membrane binding affinity and activity beyond the amino acid positions at the surface of the protein (as described in the model given in Example 5). Moreover, the specification does

not appear to provide guidance as to what amino acids may be substituted other than those that will increase the electronegativity at the protein surface.

The amount experimentation necessary to generate the large number of protein C or APC proteins encompassed by the full scope of the claims and possibly screen same for activity with a reasonable expectation of producing a protein with increased activity would be tremendous. The specification lacks direction/guidance regarding which structural features other than the amino acid positions located on the surface of the protein (the electronegativity sites, see Ex. 5) are required in order to provide the claimed activity. The working examples are only directed to amino acid substitutions at specific positions to amino acids with increased electronegativity. The nature of modifying proteins to achieve a given activity is complex. The state of the prior art establishes the unpredictability of the effects of mutation on protein structure and function. The claims, which fail to recite any limitations of what positions may be substituted and what type of amino acids may be substituted, are broader than the enabling description. Therefore, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. To practice the instant invention in a manner consistent with its full scope would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues, other than the surface amino acids, described in the specification, that may be modified to increase membrane binding and activity. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets the full scope of both the structural and functional requirements of the instant claims that constitutes undue experimentation.

*New Rejections*

***Double Patenting***

*Duplicate Claims*

Claims 67-72 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 61-66. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Conclusions***

No Claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
October 7, 2002

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER